

Remarks

This paper is responsive to the Final Office Action mailed June 10, 2011. This paper is filed with a Request for Continued Examination and a request for a three-month extension of time. Claims 1-8, 12-19, and 23-31 are pending in the instant application. In the Action, the Office rejected claims 1-8, 12-19, and 23-31. Applicant hereby amends claims 1, 7, 8, 13, 18, and 19. The amendments are fully supported by the application as filed.

Rejection – 35 U.S.C. § 112

The Office has rejected claims 1-6, 8, 12-17, 19, and 23 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. The Office states that the omitted elements are “the step of filtering out any undissolved particles, originally recited as step (c).” The Office further states that “[i]t is known in the art that undissolved particles can interfere and prevent crystallization of the desired product.” (Office Action of June 10, 2011, pages 2-3). Without addressing the merits of the rejection and in an effort to advance prosecution, Applicant has amended claims 1 and 13 to include the step of “filtering out any undissolved particles.” Applicant respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

The Office has rejected claims 1-8, 12-19, and 23-31 under 35 U.S.C. § 103(a) as being unpatentable over Farag *et al.* (Bull. Pharm. Sci. Assiut University, 1998, 21(1), 1-6) and Feldman *et al.* (Phytochemistry, 1999, 51, 867-872), in view of Pfeffer *et al.* (U.S. Patent No. 4,107,425), Experimental Organic Reactions (1957, 18, pages 504-504), and Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 44-46 and pages 120-121). The Office states that “[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to separate the alpha and beta anomers of penta-O-galloyl-D-glucose from a mixture of the alpha and beta anomers via the method as instantly claimed since analogous separations of the alpha and beta anomers of glucose derivative [sic] structurally similar to pentagalloyl glucose via crystallization using water/methanol or acetone as solvents have been

disclosed in the prior art." (Office Action of June 10, 2011, pages 7-8). Applicant respectfully traverses the rejection.

Applicant respectfully submits that Farag discloses a multi-process method for separating a mixture containing alpha and beta PGG, among other compounds. First, Farag teaches a methanol extraction step, followed by a concentrating step under reduced pressure. Next, the methanol extract undergoes fractionation with hexane, chloroform, ethyl acetate, and n-butanol, successively. In the next step, the ethyl acetate soluble fraction is subjected to reverse phase high performance liquid chromatography (HPLC) using a methanol-water solvent system as the mobile phase to afford six fractions. Finally, Farag teaches the steps of repeated purification of each of fractions V and VI via ODS column chromatography and further purification on MCI-gel CHP-20P to achieve pure beta PGG (Compound 3, 17 mg) and pure alpha PGG (Compound 4, 19 mg). Farag does not disclose, or otherwise teach or suggest, utilizing crystallization as a method for separating alpha or beta PGG from a mixture containing alpha and beta PGG. Instead, Farag teaches an extraction step, a fractionation step, a first ODS chromatography step, and repeated ODS column chromatography steps followed by purification on MCI-gel CHP-20P to finally obtain alpha and beta PGG.

Based upon the teaching of Farag, it is unclear how the Office arrives at the assertion that "there is a difference in solubility of the alpha and beta anomers of PGG in water and this can be taken advantage of for separation of two anomers from solution containing a mixture of the two anomers in water." (Office Action of June 10, 2011, page 5). Farag does not mention, either explicitly or implicitly, anything with respect to the solubility of alpha and beta PGG. Additionally, Farag utilizes a methanol-water solvent system, not just water. As discussed above, Farag teaches a multi-process method for separating alpha or beta PGG from a mixture containing alpha and beta PGG. Moreover, the most utilized process in Farag's multi-process method is reverse phase HPLC, and it is known in the art that HPLC separates compounds based upon differences in affinity or size, not solubility. Furthermore, Farag does not teach or suggest that PGG anomers can be separated based upon differences in solubility (*i.e.*, via an extraction) or by crystallization. For at least the foregoing reasons, Applicant respectfully submits that it would not have been obvious to one of ordinary skill in the art to arrive at Applicant's claimed

method based upon the multi-process method disclosed in Farag, whether read individually or in combination with any of the other cited references.

The Office states that Feldman teaches “that the individual alpha and beta anomers of PGG is [sic] separated and purified for binding studies for each anomer (page 869, Table 1).” (Office Action of June 10, 2011, page 5). Applicant respectfully submits that Feldman does not disclose any information with respect to separating alpha and beta PGG. Instead, Feldman only states that alpha and beta PGG were separately synthesized for testing their affinity for bovine serum albumin (BSA). (See Feldman at page 869, left column, first full paragraph). Applicant respectfully submits that the disclosure of Feldman is totally irrelevant to Applicant’s claimed method of separating alpha or beta PGG from a mixture containing alpha and beta PGG. For at least these reasons, Applicant respectfully submits that it would not have been obvious to one of ordinary skill in the art to arrive at Applicant’s claimed method based upon the teachings of Feldman, whether read individually or in combination with any of the other cited references.

The Office further notes that Pfeffer teaches the separation of the beta anomer of 2,3,4,6-tetra-O-benzyl-1-hexadecanoyl-D-Glucopyranose from a mixture containing an 11:89 ratio of the alpha to beta anomers via crystallization from absolute ethanol. Applicant respectfully submits that Pfeffer also teaches that attempts to separate the alpha anomer of 2,3,4,6-tetra-O-benzyl-1-hexadecanoyl-D-Glucopyranose from a mixture containing a 9:1 ratio of the alpha to beta anomers via crystallization were unsuccessful. (Pfeffer at col. 5, lines 32-40). Moreover, as seen in Table II of Pfeffer, for mixtures comprising 90% beta and 10% alpha anomers, when the ester group, R, was C₁₇H₃₅ (i.e., 2,3,4,6-tetra-O-benzyl-1-octadecanoyl-D-Glucopyranose), the mixture of the beta and alpha anomers could not be separated via crystallization. According to MPEP 2141.02 VI, “[a] prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention.” Guided by this principle, Applicant respectfully submits that Pfeffer, when considered in its entirety, teaches that separation of alpha or beta anomers from a mixture of alpha and beta anomers via crystallization is unpredictable at best. For at least these reasons, Applicant respectfully submits that it would not have been obvious to one of ordinary skill in the art to arrive at Applicant’s claimed method

based upon the disclosure of Pfeffer, whether read individually or in combination with any of the other cited references.

The Office notes that *Experimental Organic Reactions* discloses that “resolution of racemic modification (separation of anomers/optical isomers) can occur via recrystallization.” (Office Action of June 10, 2011, page 6). The Office continues by noting that *Experimental Organic Reactions* provides an example where methanol-water or acetone is used to separate racemates. Based upon the Office’s logic, methanol-water or acetone may be used to separate any and all mixtures of anomers via crystallization. Clearly this cannot be the case. Moreover, the authors of *Experimental Organic Reactions* go on to state that “the success for this method is relatively rare, … if there are some suitable conditions to give a different solubility between a racemic modification and the active substance and thus they can be resolved to some extent.” In addition to the fact that successful crystallization is rare as stated in *Experimental Organic Reactions*, the unpredictability of successfully separating alpha or beta anomers from a mixture of alpha and beta anomers via crystallization as taught by Pfeffer suggests that the claimed method of separating alpha or beta PGG from a mixture of alpha and beta PGG is nonobvious. Applicant respectfully submits that one of ordinary skill in the art reading *Experimental Organic Reactions* either individually or together with the other cited references would not find the instant claims to be obvious.

The Office relies on Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 44-46 and 120-121) to set forth the general principles involved in column chromatography and recrystallization. For example, the Office notes that “separation of compounds is based on the ability of the solvent used to selectively dissolve a substance that is to be separated” with respect to column chromatography. (Office Action of June 10, 2011, page 6). The Office further states that “[s]eparation depends on the difference in solvent power towards the substances.” (Id.). Using these two principles gleaned from Ault, the Office concludes that “[t]his indicates that the difference is [sic] solubility of substances in a solvent can be used for separating a mixture via crystallization also.” (Office Action of June 10, 2011, page 7). However, Ault notes that “[s]everal factors determine the efficiency of a chromatographic separation.” (Ault, at page 120, third paragraph). The Office seems to overlook the fact that the choice of adsorbent plays

an important role in column chromatography. Additionally, Ault even notes that “a more important property of the solvent is its ability to be itself adsorbed on the adsorbent.” (Ault, at page 120, last paragraph). Thus, an important aspect of column chromatography is the interactions between the adsorbent and the solvent, not simply the solvent. Furthermore, Ault teaches away from the use of water as a solvent by noting that “solvents to be used in column chromatography should be quite dry.” (Ault, at page 121, first full paragraph, last sentence). Taking the teachings of Ault with respect to column chromatography into consideration, it is unclear how the Office arrives at the conclusion that a particular solvent may be used to separate a mixture via crystallization. Applicant respectfully submits that Ault does not provide any particular insight into why one of ordinary skill in the art would choose crystallization with the claimed solvents to separate the particular claimed compounds.

Also, it is instructive that Farag, Feldman, and Pfeffer do not disclose the use of crystallization to separate alpha or beta PGG from a mixture of alpha and beta PGG. As previously noted, Farag discloses a multi-process method to separate alpha and beta PGG, which utilizes repeated chromatography steps of each fraction containing alpha PGG (fraction VI) and beta PGG (fraction V). With respect to Feldman, the claimed compounds (i.e., alpha and beta PGG) are mentioned, but there is no discussion of any process for separating alpha or beta PGG from a mixture of alpha and beta PGG. Moreover, Pfeffer discloses the unpredictability of separating alpha and beta anomers of benzylated glucose derivatives via crystallization. Furthermore, *Experimental Organic Reactions* merely provides an example of a specific compound (i.e., 2,4-dioxo-2,3-diethyl-5-methylpiperidine), which is totally unrelated to the claimed alpha and beta PGG compounds, that is capable of recrystallization from methanol-water or acetone. In addition, Ault simply discloses several of the general principles involved in column chromatography and recrystallization, but does not provide any suggestion or motivation as to why one of ordinary skill in the art would utilize crystallization with the claimed solvents to separate the particular claimed compounds. Applicant respectfully submits that one of ordinary skill in the art reading Farag, Feldman, Pfeffer, *Experimental Organic Reactions*, and Ault either individually or together would not find the instant claims obvious.

As for the articulated reasons as to why the claimed invention would be obvious, Applicant again respectfully disagrees with the Office's assertions. Rationale (A): The Office asserts that the instant claims combine prior art elements according to known methods to yield predictable results. The results of crystallization attempts of alpha and beta PGG are not predictable. Crystallization is a general method to separate and purify compounds, but far more often than not it cannot be applied because suitable solvents and conditions cannot be found to make compounds crystallize. Such unpredictability is found in the disclosure of Pfeffer, which shows that several attempts to separate alpha or beta anomers from a mixture of alpha and beta anomers via crystallization were unsuccessful. Rationale (C): The Office asserts that a known technique was used to improve similar devices (methods, or products) in the same way. Applicant respectfully submits that the results of the claimed methods were unexpected because of the previously known tendency of PGG to form gels (rather than crystals) in most solvents in which it dissolves. Rationale (E): The Office asserts that it was obvious to try choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. As previously stated, there is no reasonable expectation of success for crystallization (see Pfeffer at Table II; mixture of beta (90%) and alpha (10%) anomers of compound having ester group, R, equal to $C_{15}H_{31}$ crystallized from ethanol, but mixture of beta (90%) and alpha (10%) anomers of compound having ester group, R, equal to $C_{17}H_{35}$ could not be crystallized). In addition, the known high tendency of the PGG to form gels lowers the expectation of success even more. Applicant respectfully submits that for at least these reasons the claimed methods are not obvious, and respectfully requests withdrawal of the rejection.

In the event the Commissioner should decide that any additional fee or fee deficiency is due, the Commissioner is hereby authorized to charge any and all fees incurred as a result of entering or considering this document to deposit account number 03-0172.

Respectfully submitted,

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